

REMARKS

The Office Action mailed October 26, 2010, was reviewed and the comments of the Patent and Trademark Office were considered.

Claims 1 - 6, 9 - 10, 13, 15, 17 - 22 and 24 are pending in the application. Claim 7, 8, 11, 12, 14, 16 and 23 are canceled without prejudice. Claims 1 and 9 are currently amended. Support for the amendments may be found at, for example, the original specification and claims. Applicants respectfully submit that no new matter has been added by the amendments.

Withdrawal of the rejections and allowance of all pending claims are respectfully requested.

Interview Summary

Applicants appreciate the interview courteously granted to Applicants' representatives April 22, 2011. During the interview the rejections based on the Li reference were discussed as well as the proposed clarifying amendments to the claims and a declaration. The contents of the interview are incorporated into the amendments, attachments and remarks herein.

Rejections under 35 U.S.C. § 103

Claims 1 - 6, 9, 13, 15, 17, 20, 22 and 24 are rejected under 35 U.S.C. § 103(a) over Li et al. (U.S. Publication No. 2003/0035840), hereinafter "Li", in view of Sigma-Aldrich Particle Size Conversion, hereinafter "Sigma-Aldrich".

Claims 1 - 6, 9, 13, 15, 17, 20, 22 and 24 are patentable over Li in view of Sigma-Aldrich. Withdrawal of the rejection and allowance of all claims are respectfully requested.

A. Li does not disclose the combination of claimed elements that leads to the claimed release profile.

Independent claim 1, as amended, requires three claimed elements that combine to produce the claimed release profile:

1. a "weight ratio B/A is between 0.5 and 1.5";
2. "a diameter of between 200 and 800 microns"; and
3. a "single, composite coating film comprises at least one hydrophilic polymer A carrying groups that are ionized at neutral pH, and at least one hydrophobic compound B; wherein the at least one hydrophobic compound B is selected from the group consisting of hydrogenated vegetable oils, vegetable waxes, wax yellow, wax white, wax microcrystalline, lanolin, anhydrous milk fat, hard fat suppository base, lauroyl macroglycerides, cetyl alcohol, polyglyceryl diisostearate, diester or triester of glycerol with at least one fatty acid, and mixtures thereof".

These three elements combine to create the claimed release profile:

"at a constant pH of 1.4, the dissolution profile includes a latency phase with a duration less than or equal to 5 hours, and a controlled release phase following the latency phase is such

that the release time for 50% of the active principle ($t_{1/2}$) is between 0.5 hour and 35 hours, and the change from pH 1.4 to pH 6.8 results in a release phase that starts without a latency period."

Li in view of Sigma-Aldrich does not disclose this combination of elements that leads to the claimed release profile.

The composition of the coatings described in Li is unclear for one of ordinary skill in the art reading the Li specification. This lack of clarity is strengthened by a series of incorrect statements as in paragraph 0069 where water insoluble polymers are declared to be water soluble. Given the lack of clarity and description of the specification, one must refer to the examples of Li to understand the coating of the first group of pellets.

Li provides two examples. The formulations described in Examples 1 and 2 include same first group of pellets prepared according to Example 1. As such, the following discussion focuses on the coating composition of Example 1. The coating composition can be clearly understood from Example 1. The coating is composed of three components; in the following amounts:

bupropion active pellets	75%
HPMCP 50	16.9%
acetyltributyl citrate	2.5%
myvaplex 600P	5.6%

As noted by the Examiner, the coating composition shows a ratio of 5.6% of glycerol monostearate (compound B) to 16.9% of HPMCP (polymer A), i.e., a 0.33 : 1 ratio of B/A, which is less than the 0.5 to 1.5 ratio claimed. The Examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the ratio of B/A

to obtain the claimed release profile. See Office Action at page 5. Applicants respectfully disagree.

The claimed invention requires interaction of the weight ratio B/A, the particle diameter, and the coating composition as claimed to obtain the claimed release profile. It would not have been obvious to one of ordinary skill in the art at the time of the invention to modify Li as suggested by the Office Action. The release profile showed by Li in Fig. 2 is the result of a combination of two types of pellets, only one third of which has a composition as found in Li at paragraph 0065. Li does not disclose the claimed particles or the release profile obtained with only one type of pellet.

As evidence, Applicants submit herewith a Declaration of Anne-Sophie Daviaud-Venet (Daviaud-Venet Declaration). The Declaration contains three Experiments. The first two experiments use the coating composition as taught by Li in Example 1 with the weight ratio of B/A as taught by Li in Example 1 and with a particle size within the claimed range. The third experiment uses the coating composition as taught by Li in Example 1 with a weight ratio of B/A within the claimed range and with a particle size within the claimed range. These experiments must be contrasted with the Examples in the present specification, where the coating composition, the weight ratio of B/A, and the particle size are all within the claimed range.

As clearly shown, the Experiments performed using only one or two of the three claimed elements provides an immediate release profile with $t_{1/2}$ much less than 0.5 hours, which is outside the claimed release profile. Only when all three claimed elements are present, as in the Examples in the present specification, is the claimed release profile obtained.

Li does not disclose this combination of three elements as claimed that combine to produce the claimed release profile.

B. Li does not disclose any compounds overlapping those claimed for compound B

As amended, independent claim 1 does not contain any overlapping compounds with the claimed invention for compound B. Lubricants disclosed by Li are selected in the group consisting of glyceryl monostearates, Myvaplex 600P, calcium stearate or stearic acid. See Li at paragraph 0064. None of these lubricants correspond to the claimed compounds for compound B.

C. The particle size of Li is outside the claimed range.

Independent claim 1 requires microcapsules having a diameter of between 200 and 800 microns.

In the technical field of controlled release from coated particles, particle size is a main parameter that governs the rate and shape of the release profile. Particle size is an essential characteristic of the claimed invention. A coating applied to large particles, pellets or tablets, will generally not give same results on small microparticles, because relative surface area increases as diameter decreases. Indeed, relative surface area varies inversely and exponentially as diameter varies. Thus, a small reduction in diameter causes a large increase of relative surface area of the particle. As a consequence, a coating that is created for large particles or tablets will not give the same release profile when used with small particles.

In the technical field of controlled release from coated particles, particles around 500 microns are in another category compared to particles over 1 mm, which are classic "pellets". The best practical example of this difference in behavior is enteric polymers. These polymers are known and effective to create delayed release (no release in acidic pH and release in neutral pH). A coating of about 5% over a tablet (over 1 mm) is sufficient to obtain this effect. When used with small particles (around 500 microns), it is not possible to obtain absence of release in

acidic pH unless applying a significant amount of coating, leaving little to no place in the particle for the active principle. This is due to the large surface area on the smaller particle and to the minimum thickness of the coating needed to obtain the effect. Using a coating developed for a large particle to coat small particles will not give the same results or predictable results.

Applicants submit herewith a Declaration of Catherine Castan describing a size calculation for particles disclosed in Li's example 1 where a minimum final particle diameter is 1000 microns. Specifically, Li starts from inert cores having a diameter which is 30 to 35 mesh, which corresponds to 595 to 500 microns, respectively. The size of the starting inert core must not be confused with the size of the finished coated pellets.

Li applies a large amount of materials to the inert cores, as found in Example 1 of Li: 2.8 kg of bupropion HCl + 0.14 kg of hydroxypropyl methylcellulose = 2.94 kg of material applied to 1.06 kg of inert core. See Li at paragraph 0077. This addition of materials to the inert core represents a gain of mass of 277%, which results in the diameter of the resultant particles increased significantly. It is straightforward to calculate the final particle diameter obtained by Li because Li starts from round shaped sugar spheres with well-defined particle sizes. The minimum final diameter obtained is 1000 microns. As the instant application claims particle size of coated microparticles between 200 and 800 μm , this minimum final diameter is outside the claimed range.

Even if Li suggests that he could have started with smaller inert cores (see Li at paragraph 0054), the experiments shown in the Declaration of Anne Sophie Venet Daviaud show that he would not have obtained the claimed release profile.

D. Conclusion

To summarize, Li does not disclose the three claimed elements that combine to create the claimed release profile. Additionally, Li does not disclose any of the compounds claimed for the hydrophobic compound B. Furthermore, Li does not disclose final particle diameters within the claimed range.

For at least these reasons, independent claim 1 is patentable over Li in view of Sigma-Aldrich. Dependent claims 2 - 6, 9, 13, 15, 17, 20, 22 and 24 depend from independent claim 1 and add further patentable features to the patentable features of the independent claim. Thus, claims 1 - 6, 9, 10, 13 - 15, 17, 20, 22 and 24 are patentable over the cited references.

Withdrawal of the rejection and allowance of all claims are respectfully requested.

Claims 1 - 6, 9, 13, 15, 17, 20 - 22 and 24 are rejected under 35 U.S.C. § 103(a) over Li in view of Sigma-Aldrich and further in view of Dante (U.S. Patent No. 6,034,091), hereinafter "Dante".

Independent claim 1 is patentable over Li in view of Sigma-Aldrich as described above. Dependent claims 2 - 6, 9, 13, 15, 17, 20 - 22 and 24 depend from independent claim 1 and add further patentable features to the patentable features of the independent claim. Thus, claims 1 - 2 - 6, 9, 13, 15, 17, 20 - 22 and 24 are patentable over the cited references. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Claims 1 - 6, 9, 13, 15, 17 - 20, 22 and 24 are rejected under 35 U.S.C. § 103(a) over Li in view of Sigma-Aldrich and further in view of Ishibashi (EP Patent No. 1101490), hereinafter "Ishibashi".

Independent claim 1 is patentable over Li in view of Sigma-Aldrich as described above. Dependent claims 2 - 6, 9, 13, 15, 17 - 20, 22 and 24 depend from independent claim 1 and add

further patentable features to the patentable features of the independent claim. Thus, claims 1 - 2 - 6, 9, 13, 15, 17 - 20, 22 and 24 are patentable over the cited references. Withdrawal of the rejection and allowance of all claims are respectfully requested.

Claims 1 - 6, 9, 10, 13 - 15, 17, 20, 22 and 24 are rejected under 35 U.S.C. § 103(a) over Li in view of Sigma-Aldrich and further in view of Seth (U.S. Patent No. 6,096,341), hereinafter "Seth".

Independent claim 1 is patentable over Li in view of Sigma-Aldrich as described above. Dependent claims 2 - 6, 9, 10, 13 - 15, 17, 20, 22 and 24 depend from independent claim 1 and add further patentable features to the patentable features of the independent claim. Thus, claims 1 - 2 - 6, 9, 10, 13 - 15, 17, 20, 22 and 24 are patentable over the cited references. Withdrawal of the rejection and allowance of all claims are respectfully requested.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. Entry of this amendment and an early notice to this effect is earnestly solicited. Should there be any questions regarding this application, the Examiner is invited to contact the undersigned at the number shown below.

Applicants submit herewith a request for a three month extension of time and the corresponding fee. If additional fees or extensions are due, please charge our Deposit Account No. 50-2228, under Order Number 022290.0116C1US.

Dated: April 26, 2011

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